STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 138733

TO: Andrew D Kosar
Location: REM 3C18/3C04
Art Unit: 1654
November 26, 2004

Case Serial Number: 10/663220

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

Access DB# 138733

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: **Andrew D. Kosar** Examiner# : **80341** Date: **11/19/04**

Art Unit: **1654** Phone Number: **(571)272-0913** Serial Number: **10/663,220**

Mail Box and Bldg/Room Location: **Mail: REM 3c18** Results Format Preferred (circle): **Paper** Disk E-mail
Office: REM 3c04

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If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

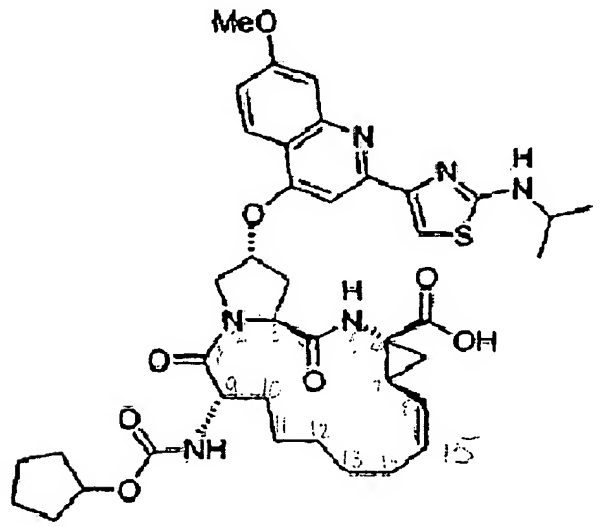
Title of Invention: Potent inhibitor of HCV serine protease

Inventors (please provide full names): Shirlynn Chen; Jens Oliver Croenlein; Gerhard Nehmiz; Gerhard Steinmann; Jocelyn Abella Gunn; Phuong Do Costa

Earliest Priority Filing Date: 09/30/2002

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following compound:



If found, Please search as:

1) as a pharmaceutical composition
   A) alone or
   B) in combination with antivirals (against HIV, HCV, HAV)
2) Also, broadly methods of use/treatment of viruses (HIV, HCV, HAV, HBV) (if compounds are found)

Thank you.

****

STAFF USE ONLY

Searcher: Shefpaine
Searcher Phone: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 11/26/04
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: _____

Type of search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Full Text _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN _____
Dialog _____
Questel/Orbit _____
Dr. Link _____
Lexis/Nexis _____
Sequence System _____
WWW/Internet _____
Other (specify) _____

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FILE 'HCAPLUS' ENTERED AT 10:32:46 ON 26 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 26 Nov 2004  VOL 141 ISS 22
FILE LAST UPDATED: 24 Nov 2004  (20041124/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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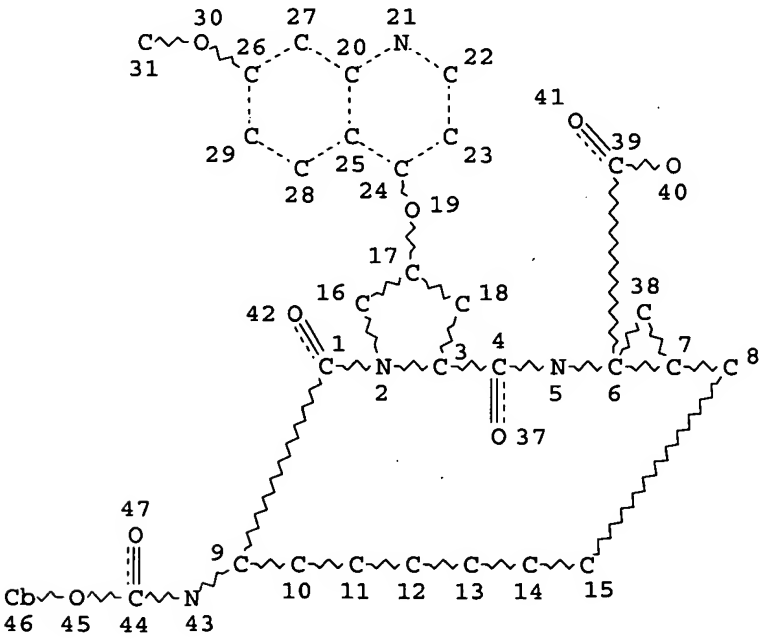

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS  42
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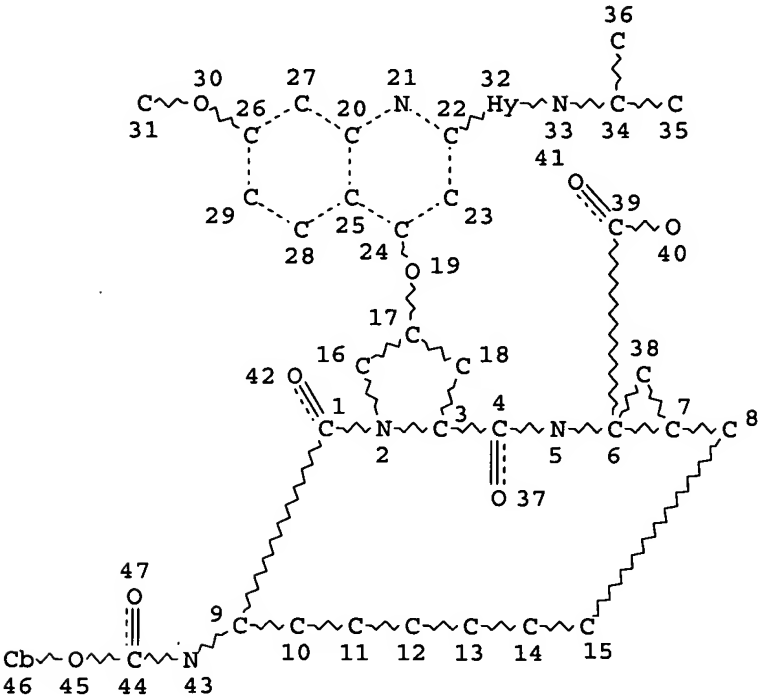
L6 STR



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NUMBER OF NODES IS 47

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L8 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:940427 HCAPLUS
TITLE: The design of a potent inhibitor of the hepatitis C virus NS3 protease: BILN 2061 - From the NMR tube to the clinic
AUTHOR(S): Tsantrizos, Youla S.
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Biopolymers (2004), 76(4), 309-323
CODEN: BIPMAA; ISSN: 0006-3525
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The virally encoded serine protease NS3/NS4A is essential to

the life cycle of the hepatitis C virus (HCV), an important human pathogen causing chronic hepatitis, cirrhosis of the liver, and hepatocellular carcinoma. Until very recently, the design of inhibitors for the HCV NS3 protease was limited to large peptidomimetic compds. with poor pharmacokinetic properties, making drug discovery an extremely challenging endeavor. In our quest for the discovery of a small-mol. lead that could block replication of the hepatitis C virus by binding to the HCV NS3 protease, the critical protein-polypeptide interactions between the virally encoded NS3 serine protease and its polyprotein substrate were investigated. Lead optimization of a substrate-based hexapeptide, guided by structural data, led to the understanding of the mol. dynamics and electronic effects that modulate the affinity of peptidomimetic ligands for the active site of this enzyme. Macrocyclic β-strand scaffolds were designed that allowed the discovery of potent, highly selective, and orally bioavailable compds. These mols. were the first HCV NS3 protease inhibitors reported that inhibit replication of HCV subgenomic RNA in a cell-based replicon assay at low nanomolar concns. Optimization of their biopharmaceutical properties led to the discovery of the clin. candidate BILN 2061. Oral administration of BILN 2061 to patients infected with the hepatitis C genotype 1 virus resulted in an impressive reduction of viral RNA levels, establishing proof-of-concept for HCV NS3 protease inhibitors as therapeutic agents in humans.

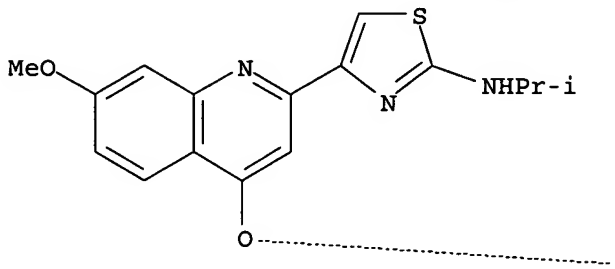
IT **300832-84-2**, BILN 2061
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design of potent inhibitor of hepatitis C virus NS3 protease BILN 2061: from NMR tube to clinic)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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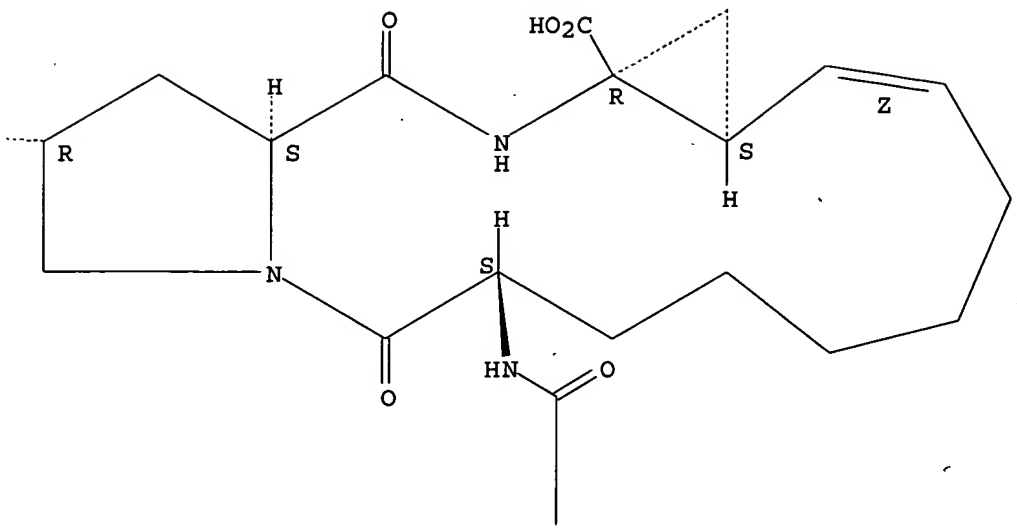

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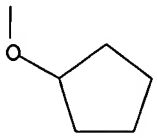


REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:927080 HCAPLUS
TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors
INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui; Wang, Zeren
PATENT ASSIGNEE(S): Boehringer Ingelheim International, G.m.b.H., Germany
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093915	A1	20041104	WO 2004-US8837	20040323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004229776 A1 20041118 US 2004-807023 20040323
PRIORITY APPLN. INFO.: US 2003-459765P P 20030402

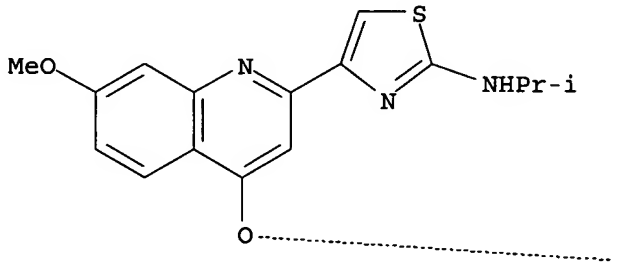
AB Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. are lipid based systems and comprise the hepatitis C viral protease inhibitor together with at least one pharmaceutically acceptable amine, at least one pharmaceutically acceptable base, at least one pharmaceutically acceptable oil and optionally one or more addnl. ingredients. For example, a formulation was prepared containing hepatitis C protease inhibitor 10, tromethamine 1, sodium hydroxide 0.3, water 1.7, ethanol 10, propylene glycol 5, α-tocopherol 0.4, Capmul MCM 22, and TPGS 49.6%, resp. The formulation can be filled into hard shell or soft gelatin capsules.

IT **300832-84-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. for hepatitis C viral protease inhibitors)

RN 300832-84-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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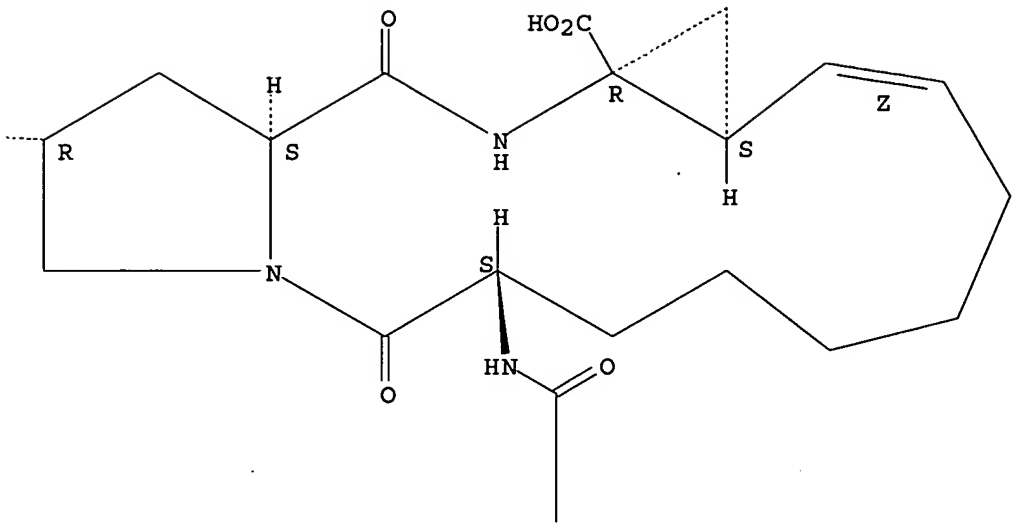

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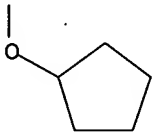

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:905774 HCAPLUS
TITLE: Process for preparing macrocyclic compounds
INVENTOR(S): Donsbach, Kai; Ecker, Dieter; Frutos, Rogelio Perez; Gallou, Fabrice; Gutheil, Dieter; Haddad, Nizar; Hagenkoetter, Robert; Kemmer, Dirk; Kroeber, Jutta; Nicola, Thomas; Schnaubelt, Juergen; Schul, Michael; Simpson, Robert Donald; Wei, Xudong; Winter, Eric; Xu, Yibo; Yee, Nathan K.; Brandenburg, Joerg
PATENT ASSIGNEE(S): Boehringer Ingelheim International, G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092203	A2	20041028	WO 2004-US10476	20040406

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-461662P P 20030410

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed is a process for preparing macrocyclic compds. I [W is CH or N; R1 is H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy or an amino group; R2 is H, halo, alkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, (un)substituted cycloalkyl, aryl or heterocyclyl; R3 is OH, NH2, aryl-, heteroaryl- or acylamino; D is alkylene which may be substituted by R4 (alkyl, alkoxy, halo, amino, etc.); A is CO2H or an amide or salt] which are potent active agents for the treatment of hepatitis C virus (HCV) infection. The process involves reaction of a 4-hydroxyproline sulfonate macrocycle with a 4-naphthol or 4-quinolinol derivative and was applied to the synthesis of II by a multistep sequence.

IT **681145-22-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing macrocyclic compds.)

RN 681145-22-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

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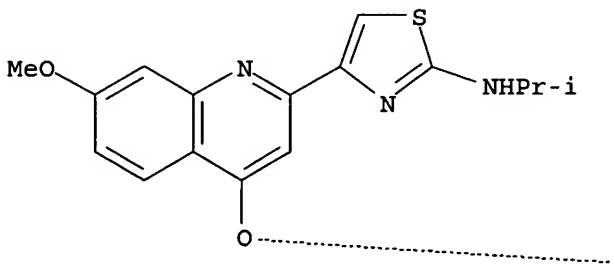

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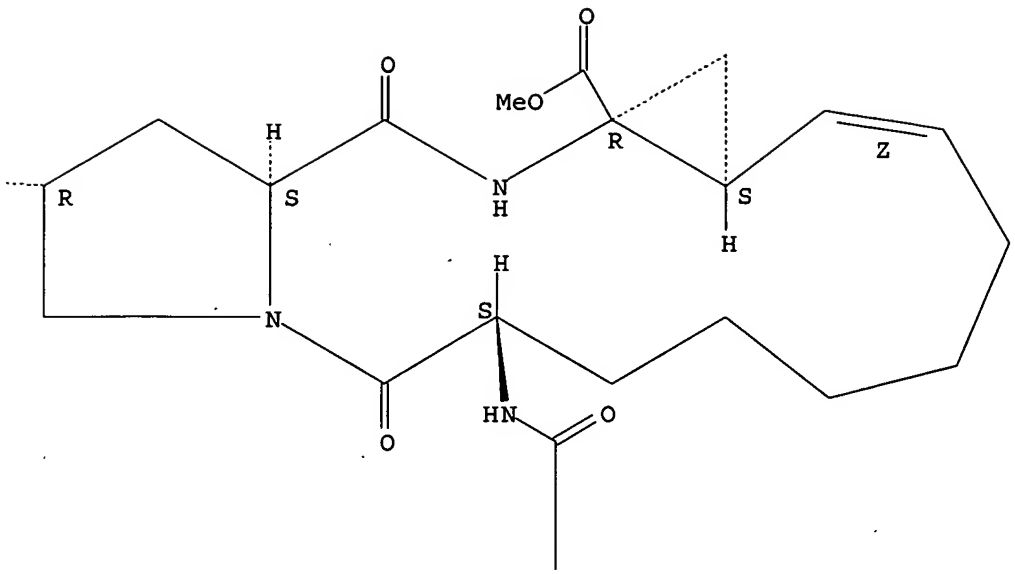

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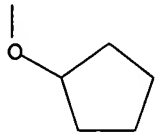


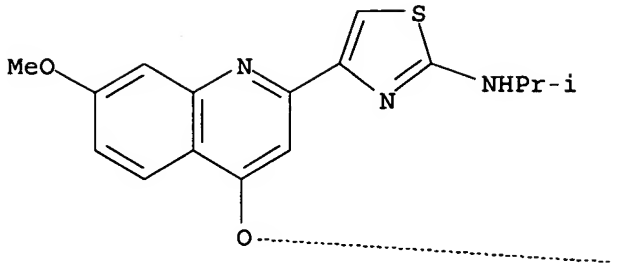
IT **300832-84-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing macrocyclic compds.)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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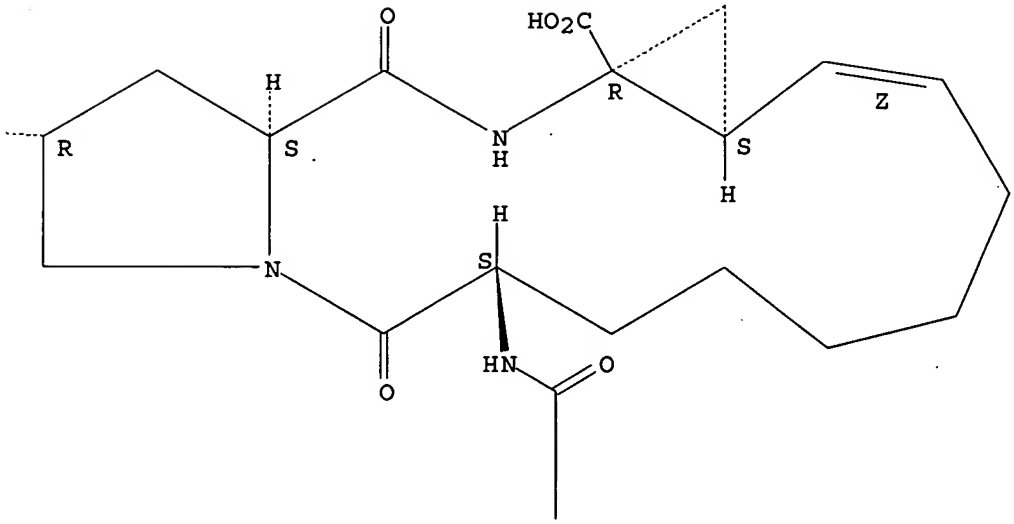

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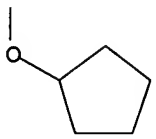

L8 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:857622 HCAPLUS
DOCUMENT NUMBER: 141:337786
TITLE: Crystalline phases of a potent HCV inhibitor
INVENTOR(S): Cerreta, Michael Kenneth; Smoliga, John Andrew; Varsolona, Richard J.
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087741	A1	20041014	WO 2004-US9085	20040325
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004229777	A1	20041118	US 2004-809597	20040325

PRIORITY APPLN. INFO.: US 2003-458188P P 20030327
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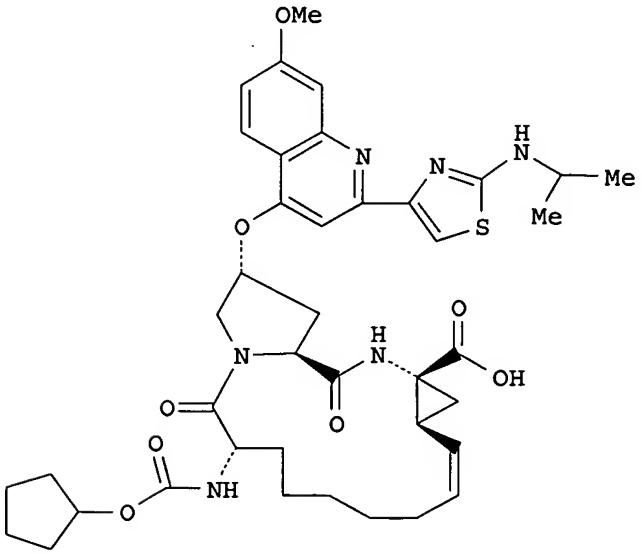


I

AB This invention relates to novel crystalline phases of Compound (I), methods for the preparation thereof, pharmaceutical compns. thereof, and their use in the treatment of Hepatitis C Viral (HCV) infection.

IT **300832-84-2P**
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(crystalline phases of a potent HCV inhibitor)

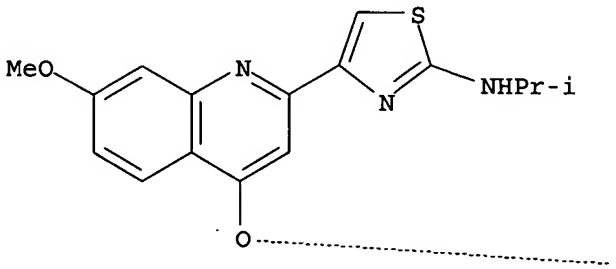
RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16

,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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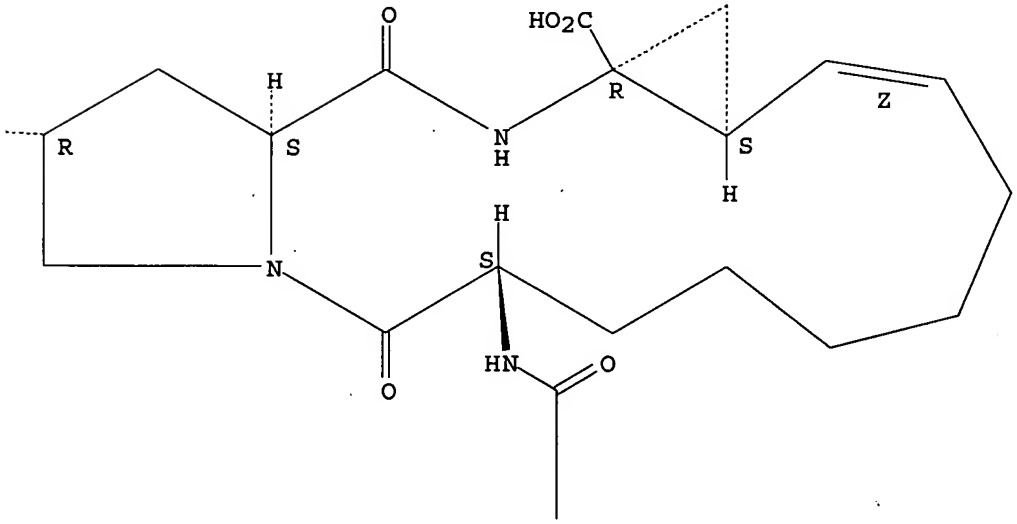

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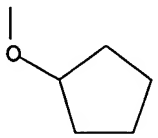


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:590266 HCAPLUS
DOCUMENT NUMBER: 141:184653
TITLE: Sensitivity of NS3 serine proteases from hepatitis C virus genotypes 2 and 3 to the inhibitor BILN 2061
AUTHOR(S): Thibeault, Diane; Bousquet, Christiane; Gingras, Rock; Lagace, Lisette; Maurice, Roger; White, Peter W.; Lamarre, Daniel
CORPORATE SOURCE: Department of Biological Sciences, Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Virology (2004), 78(14), 7352-7359
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

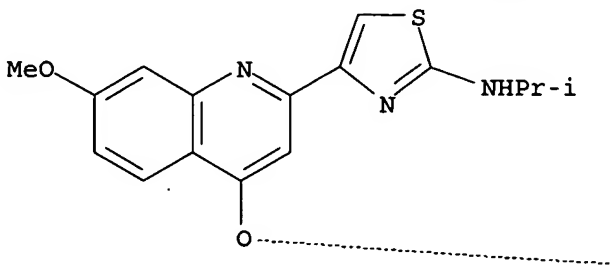
AB Hepatitis C virus (HCV) displays a high degree of genetic variability. Six genotypes and more than 50 subtypes have been identified to date. In this report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac, 2b, and 3a, revealing no major differences in activity. In vitro sensitivity studies with BILN 2061 showed a decrease in affinity for proteases of genotypes 2 and 3 (Ki, 80 to 90 nM) compared to genotype 1 enzymes (Ki, 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to BILN 2061, active-site residues in the proximity of the inhibitor binding site were replaced in the genotype-1b enzyme with the corresponding genotype-2b or -3a residues. The replacement of five residues at positions 78, 79, 80, 122, and 132 accounted for most of the reduced sensitivity of genotype 2b, while replacement of residue 168 alone could account for the reduced sensitivity of genotype 3a. BILN 2061 remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with Ki values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for BILN 2061 as an antiviral agent for individuals infected with non-genotype-1 HCV.

IT **300832-84-2**, BILN 2061
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor BILN 2061)

RN 300832-84-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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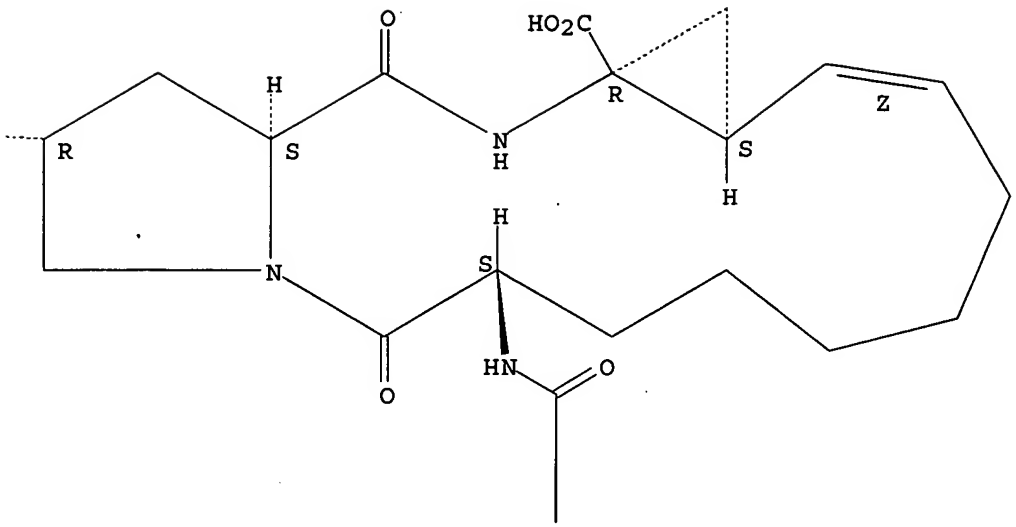

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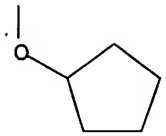
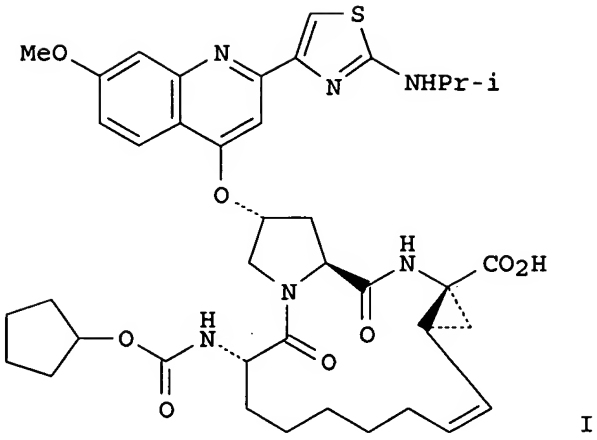


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:580783 HCAPLUS
DOCUMENT NUMBER: 141:261053
TITLE: Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans
AUTHOR(S): Faucher, Anne-Marie; Bailey, Murray D.; Beaulieu, Pierre L.; Brochu, Christian; Duceppe, Jean-Simon; Ferland, Jean-Marie; Ghiro, Elise; Gorys, Vida; Halmos, Ted; Kawai, Stephen H.; Poirier, Martin; Simoneau, Bruno; Tsantrizos, Youla S.; Llinas-Brunet, Montse
CORPORATE SOURCE: Chemistry Department, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Organic Letters (2004), 6(17), 2901-2904
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of BILN 2061 (I), a hepatitis C virus (HCV) NS3 protease inhibitor with proven antiviral effect in humans, was accomplished in a convergent manner from four building blocks. The procedure described here was suitable for the preparation of multigram quantities of BILN 2061 for preclin. pharmacol. evaluation.

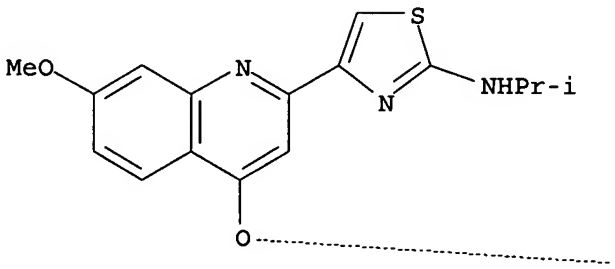
IT **300832-84-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidyl macrocycle BILN-2061, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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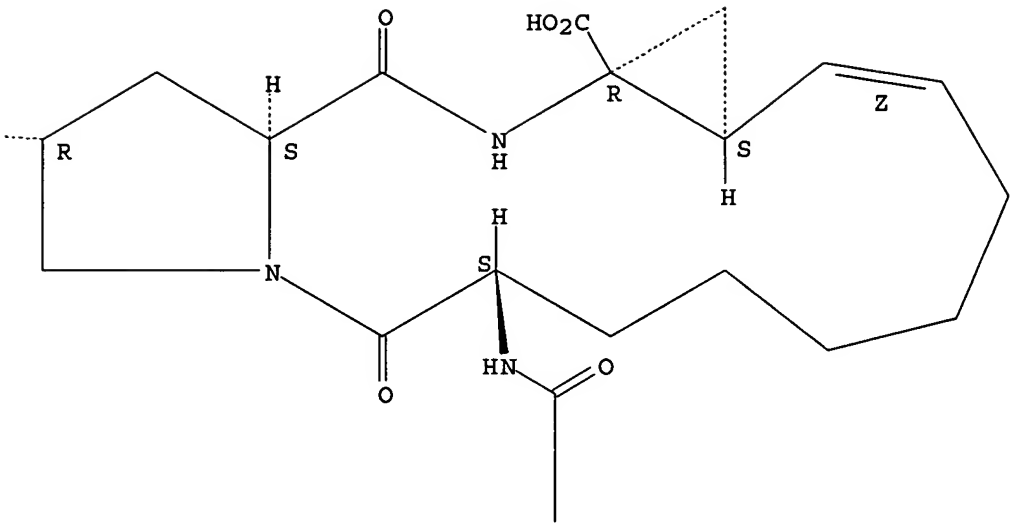

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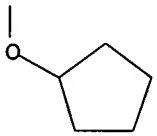


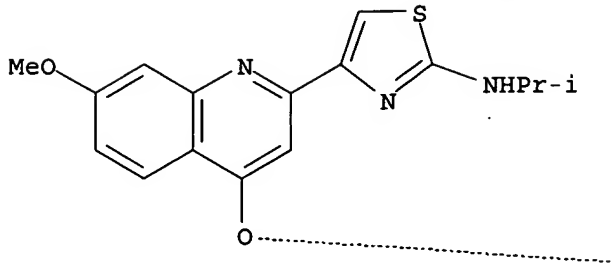
IT **681145-22-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidyl macrocycle BILN-2061, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

RN 681145-22-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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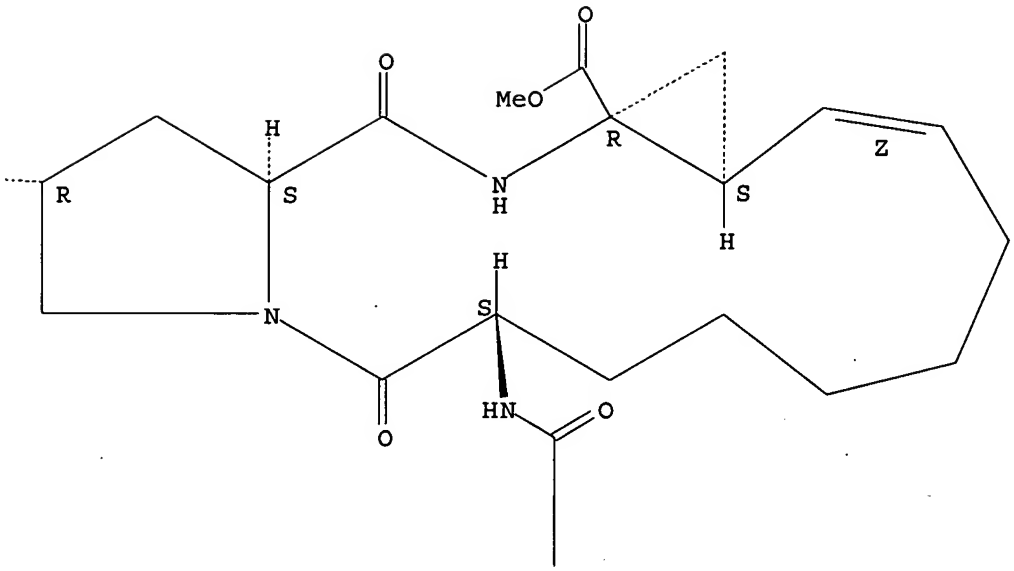

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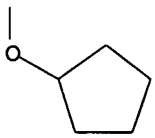


REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:468978 HCAPLUS
DOCUMENT NUMBER: 141:220806
TITLE: Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro
AUTHOR(S): Lu, Liangjun; Pilot-Matias, Tami J.; Stewart, Kent D.;

Randolph, John T.; Pithawalla, Ron; He, Wenping; Huang, Peggy P.; Klein, Larry L.; Mo, Hongmei; Molla, Akhteruzzaman
CORPORATE SOURCE: Antiviral Research, Global Pharmaceutical Research and Development, Abbott Park, IL, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(6), 2260-2266
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BILN 2061 is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clin. investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of drug-resistant viruses in treated patients. The development of resistance to BILN 2061 was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concns. of BILN 2061 for these colonies were 72- to 1228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Mol. clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold redns. in susceptibility to BILN 2061, resp., compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure anal. of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

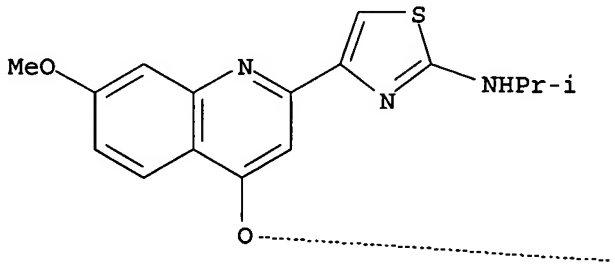
IT **300832-84-2**, BILN 2061
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mutations conferring inhibitor resistance on hepatitis C virus serine protease)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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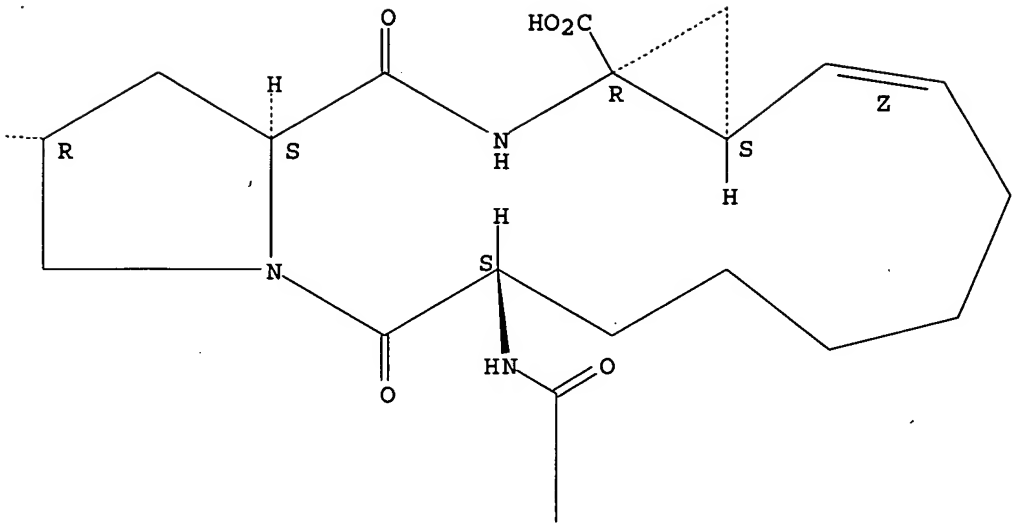
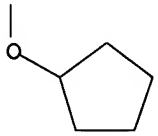


PAGE 2-B



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392478 HCAPLUS
DOCUMENT NUMBER: 140:400031
TITLE: Macrocyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses
INVENTOR(S): Lamarre, Daniel; Lagace, Lisette
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039833	A1	20040513	WO 2003-CA1634	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,

OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-421900P P 20021029
US 2003-442769P P 20030127

OTHER SOURCE(S): MARPAT 140:400031

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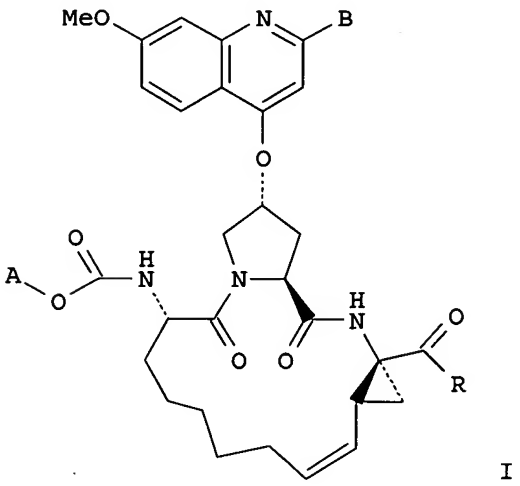


I

AB The invention relates to macrocyclic compds. I [A is alkyl or cycloalkyl; B is Ph or thiazolyl, which may be substituted by alkylamino or alkanoylamino; R is OH or NHSO2R2, where R2 is (un)substituted alkyl, cycloalkyl or aryl] or their pharmaceutically-acceptable salts for the treatment of a mammal infected with a virus of the Flaviviridae family. Thus, IC50 values for compound I [A is cyclopentyl, B is 2-(isopropylamino)-4-thiazolyl, R is OH] against HCV NS3-NS4A protease are shown graphically.

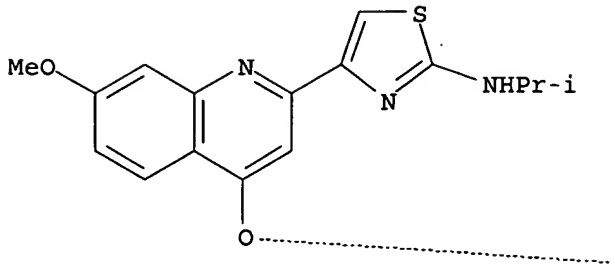
IT **300832-84-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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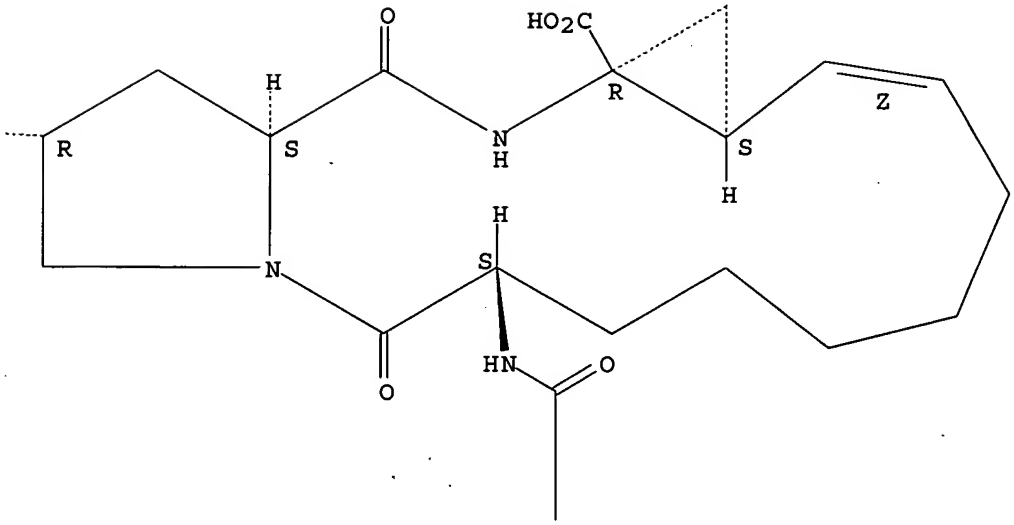

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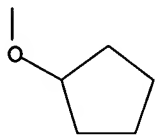

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:370958 HCAPLUS
DOCUMENT NUMBER: 140:357673
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Llinas-Brunet, Montse; Bailey, Murray D.

PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.h., Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037855	A1	20040506	WO 2003-CA1604	20031020

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
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US 2002-433820P	P	20021216
US 2003-442768P	P	20030127

OTHER SOURCE(S): MARPAT 140:357673
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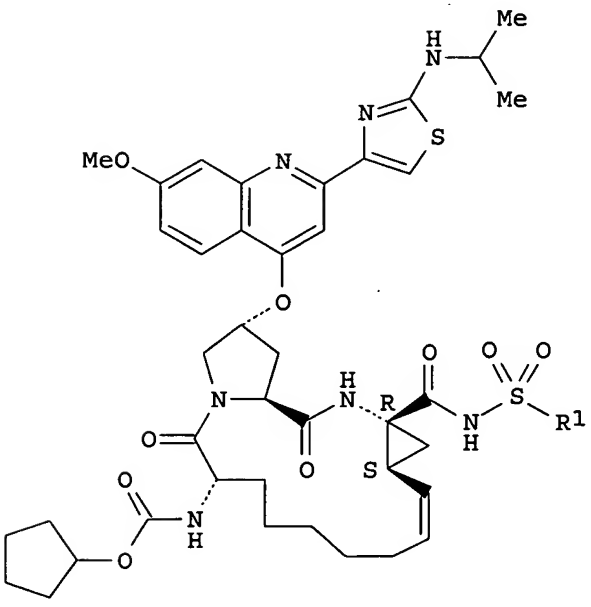


I

AB Macrocyclic peptides I [R1 is (un)substituted alkyl, cycloalkyl, alkylcycloalkyl, aryl or heteroaryl] or their pharmaceutically-acceptable salts were prepared as inhibitors of the hepatitis C virus (HCV) NS3 protease. Thus, I (R = Me) was prepared by a multistep sequence involving peptide coupling, olefin metathesis to form the macrocycle and methanesulfonamidation.

IT **300832-84-2P 681145-22-2P**

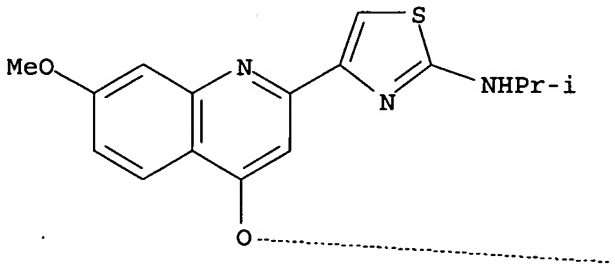
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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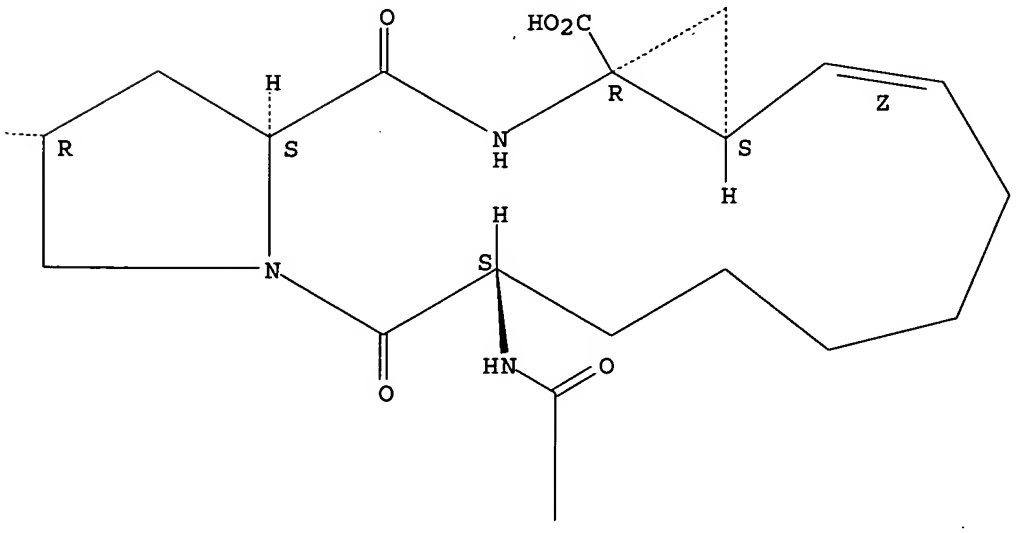

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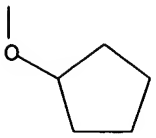
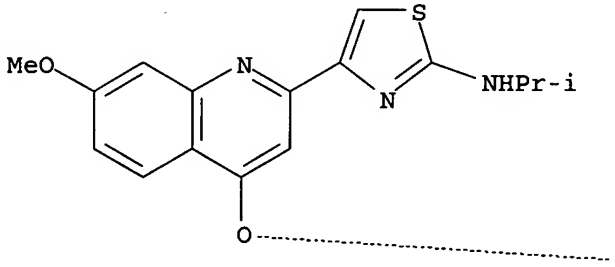


RN 681145-22-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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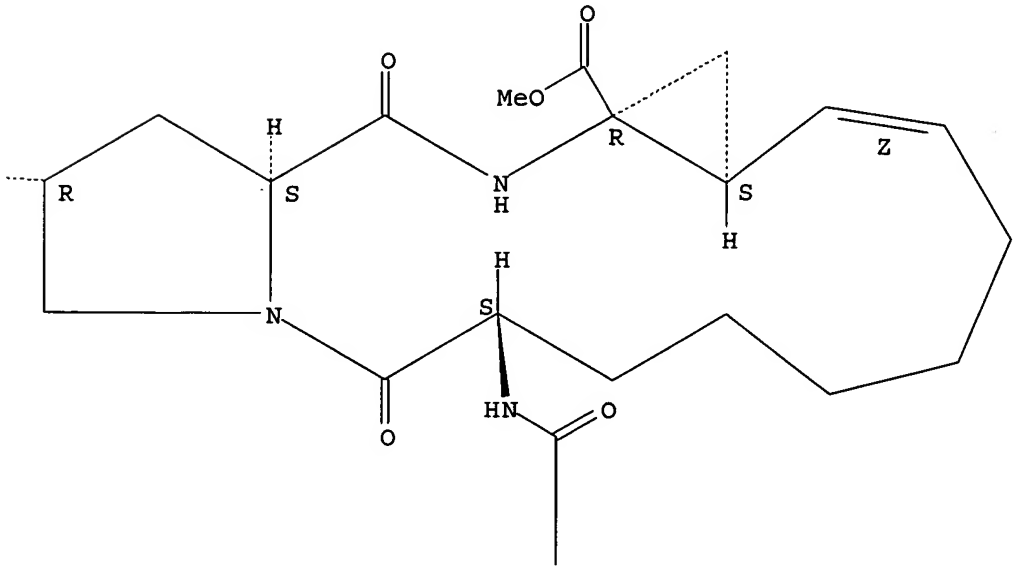
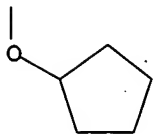


PAGE 2-B



L8 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:325457 HCAPLUS
DOCUMENT NUMBER: 141:16899
TITLE: In Vitro Resistance Studies of Hepatitis C Virus Serine Protease Inhibitors, VX-950 and BILN 2061: structural analysis indicates different resistance mechanisms
AUTHOR(S): Lin, Chao; Lin, Kai; Luong, Yu-Ping; Rao, B. Govinda; Wei, Yun-Yi; Brennan, Debra L.; Fulghum, John R.; Hsiao, Hsun-Mei; Ma, Sue; Maxwell, John P.; Cottrell, Kevin M.; Perni, Robert B.; Gates, Cynthia A.; Kwong, Ann D.
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, 02139, USA
SOURCE: Journal of Biological Chemistry (2004), 279(17), 17508-17514
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

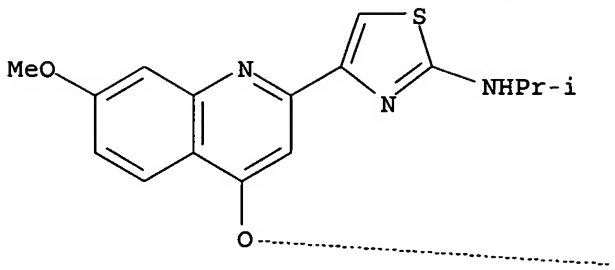
AB We have used a structure-based drug design approach to identify small mol. inhibitors of the hepatitis C virus (HCV) NS3·4A protease as potential candidates for new anti-HCV therapies. VX-950 is a potent NS3·4A protease inhibitor that was recently selected as a clin. development candidate for hepatitis C treatment. In this report, we describe in vitro resistance studies using a subgenomic replicon system to compare VX-950 with another HCV NS3·4A protease inhibitor, BILN 2061, for which the Phase I clin. trial results were reported recently. Distinct drug-resistant substitutions of a single amino acid were identified in the HCV NS3 serine protease domain for both inhibitors. The resistance conferred by these mutations was confirmed by characterization of the mutant enzymes and replicon cells that contain the single amino acid substitutions. The major BILN 2061-resistant mutations at Asp168 are fully susceptible to VX-950, and the dominant resistant mutation against VX-950 at Ala156 remains sensitive to BILN 2061. Modeling anal. suggests that there are different mechanisms of resistance to VX-950 and BILN 2061.

IT **300832-84-2**, BILN 2061
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061)

RN 300832-84-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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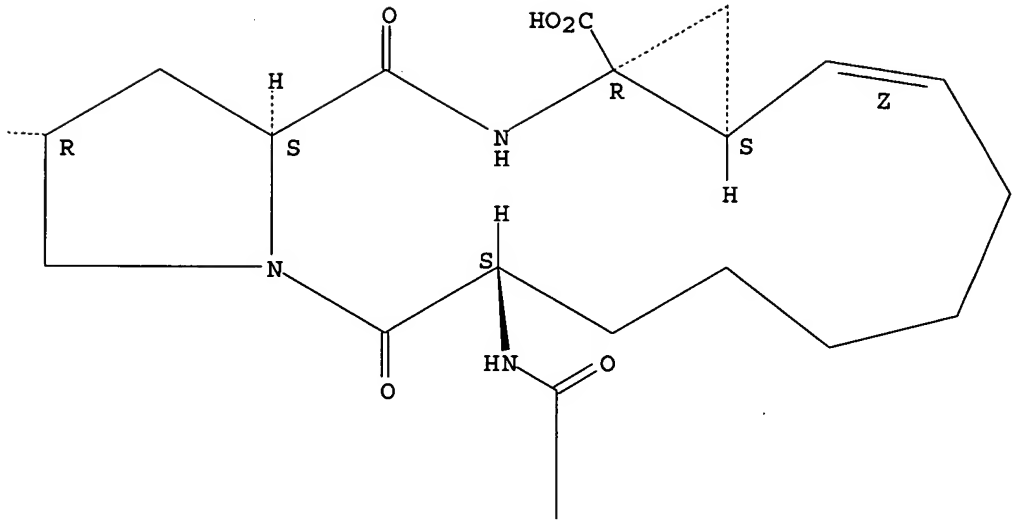

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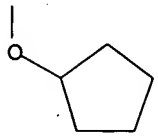

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:310970 HCAPLUS
DOCUMENT NUMBER: 140:327091
TITLE: Potent inhibitor of HCV serine protease
INVENTOR(S): Chen, Shirlynn; Nehmiz, Gerhard; Croenlein, Jens Oliver; Steinmann, Gerhard; Gunn, Jocelyn Abella; Costa, Phuong Do

PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004030670	A1	20040415	WO 2003-US30402		20030925
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004138109	A1	20040715	US 2003-663220		20030916
PRIORITY APPLN. INFO.:			US 2002-414940P	P	20020930
			US 2002-421904P	P	20021029
			US 2002-433834P	P	20021216
			US 2003-443662P	P	20030130

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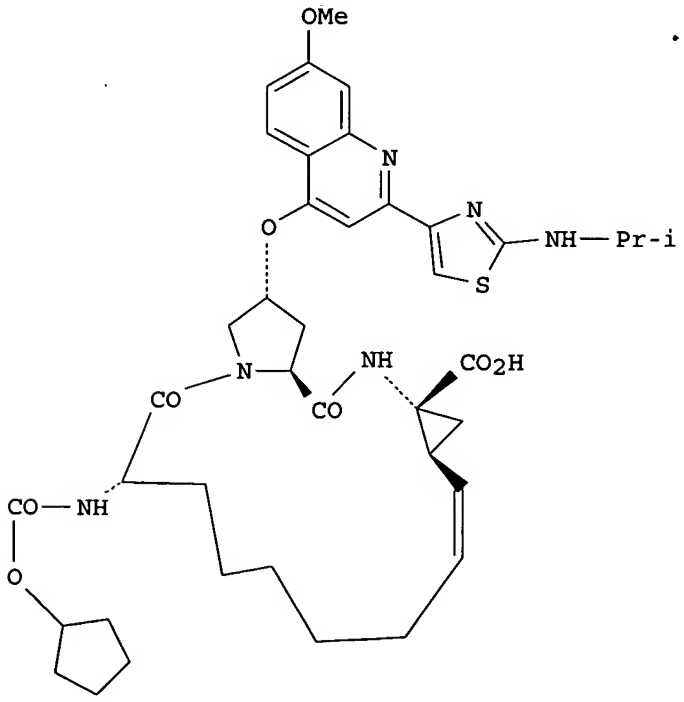


I

AB Disclosed are oral pharmaceutical compns., kits and methods of treating and preventing Hepatitis C Viral (HCV) infections wherein Compound (I), a

potent inhibitor of HCV serine protease, or a pharmaceutically acceptable salt thereof, is administered in a selected dosage range. Also disclosed are the use of I or a pharmaceutically acceptable salt thereof, as a control substance for validating an HCV replication assay and also as a control substance for determining the relative effectiveness of one or more substances, alone or in combination, to inhibit the replication of HCV.

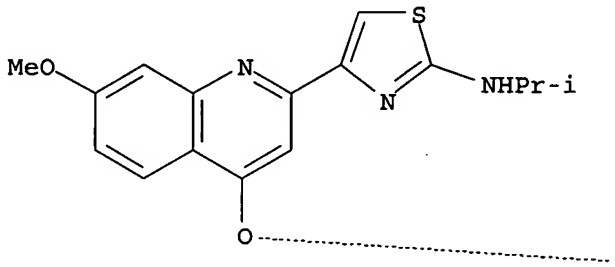
IT **300832-84-2**
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(potent inhibitor of HCV serine protease)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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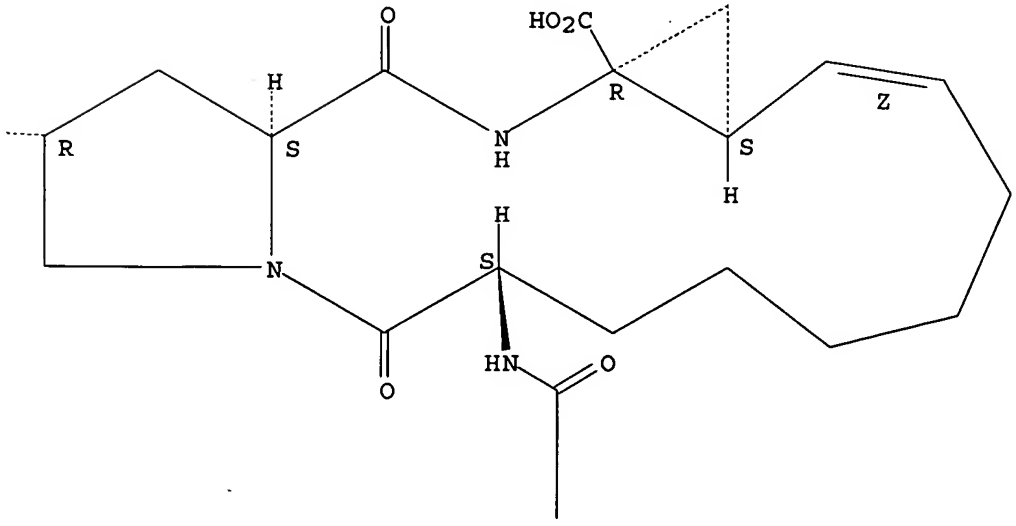
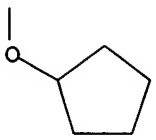


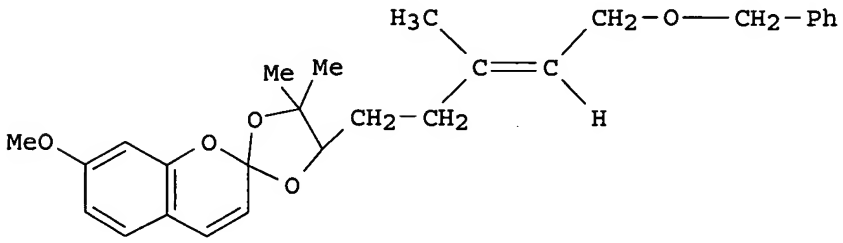


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:252197 HCAPLUS
DOCUMENT NUMBER: 140:281350
TITLE: Spiro compounds for inhibiting the first-pass effect
INVENTOR(S): Harris, James W.
PATENT ASSIGNEE(S): Bioavailability System, LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S. Ser. No. 793,416.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058982	A1	20040325	US 2003-422848	20030425
US 6248776	B1	20010619	US 1999-251467	19990217
US 6476066	B1	20021105	US 2001-793416	20010227
PRIORITY APPLN. INFO.:			US 1999-251467 A3	19990217
			US 2001-793416 A2	20010227
			US 1997-56382P P	19970826
			US 1997-997259 A2	19971223

OTHER SOURCE(S): MARPAT 140:281350
GI



I

AB Compns., methods, etc. for addressing the first-pass effect are presented. An example compound prepared was I. Also processing citrus oils to obtain the compds. is given as examples as well as assessment of human cytochrome P 450-mediated biotransformation.

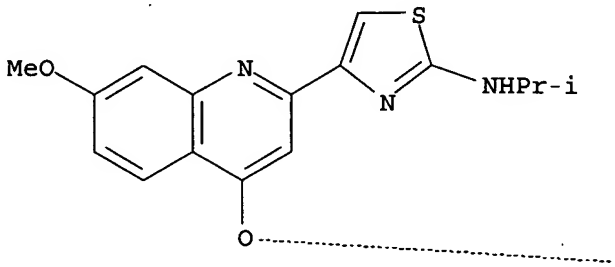
IT **300832-84-2**, BILN 2061
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spiro compds. for inhibiting the first-pass effect)

RN 300832-84-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic

acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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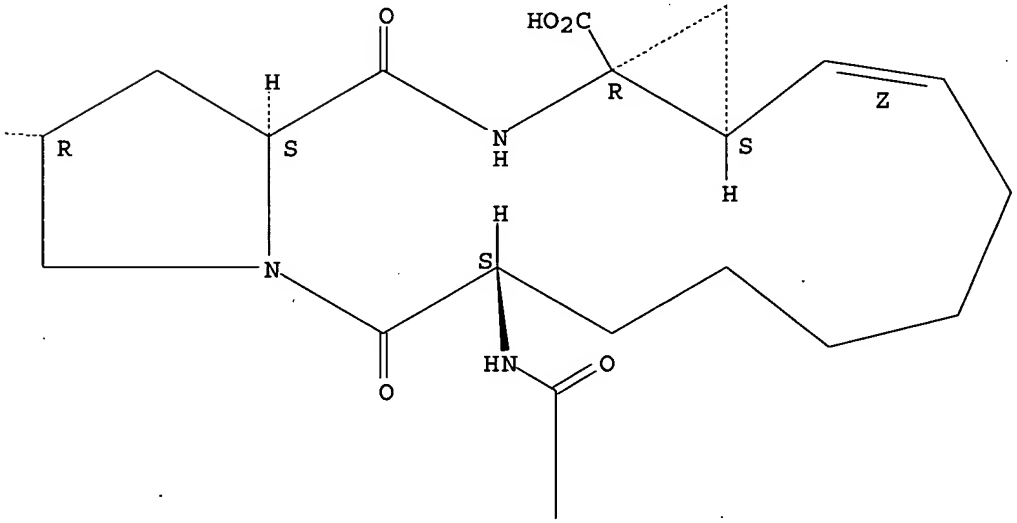

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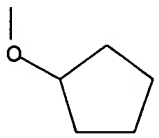


L8 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:168624 HCAPLUS
DOCUMENT NUMBER: 140:350045
TITLE: Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of BILN 2061
AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray D.; Bolger, Gordon; Brochu, Christian; Faucher, Anne-Marie; Ferland, Jean Marie; Garneau, Michel; Ghiro, Elise; Gorys, Vida; Grand-Maitre, Chantal; Halmos, Ted; Lapeyre-Paquette, Nicole; Liard, Francine; Poirier, Martin; Rheaume, Manon; Tsantrizos, Youla S.; Lamarre, Daniel
CORPORATE SOURCE: Departments of Chemistry and Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Medicinal Chemistry (2004), 47(7), 1605-1608
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

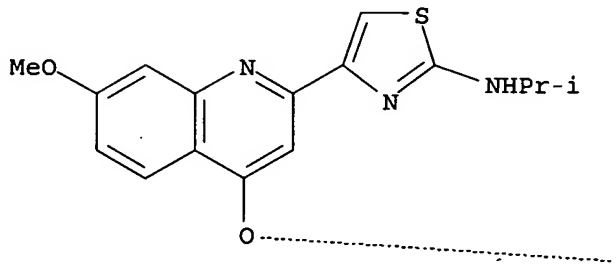
AB From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease macrocyclic inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. BILN 2061 was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

IT **300832-84-2P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(BILN 2061; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of BILN 2061)

RN 300832-84-2 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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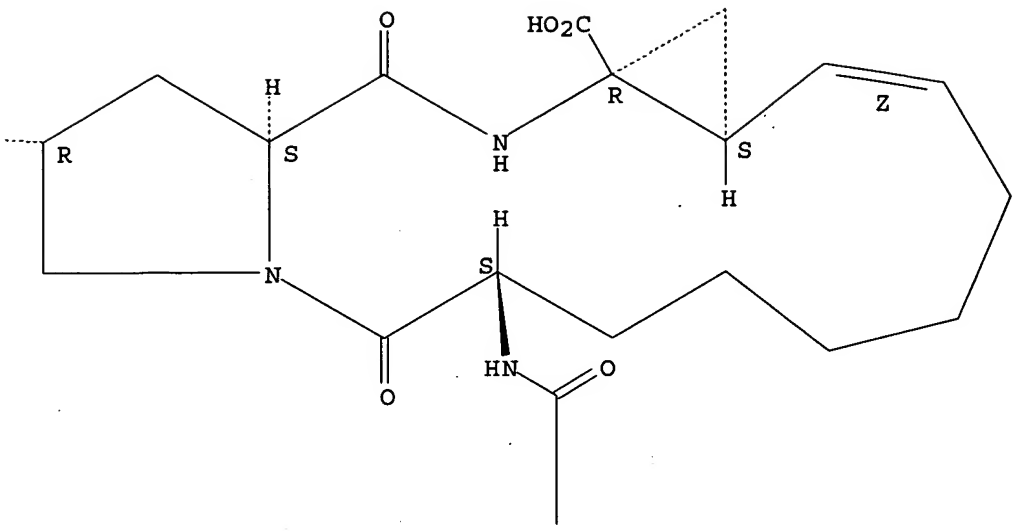

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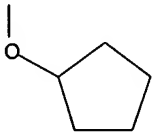

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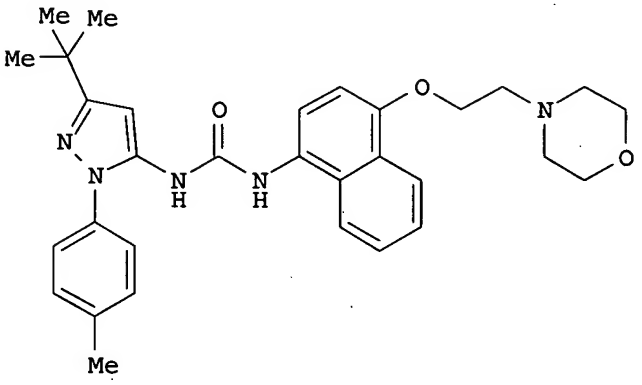
L8 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:142968 HCAPLUS
DOCUMENT NUMBER: 140:193056
TITLE: Combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compositions, and use in the treatment of cytokine-mediated diseases
INVENTOR(S): Simianer, Stefan; Bilbault, Pascal; Cappola, Michael L.; Way, Susan Lynn
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA; Boehringer Ingelheim France
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014387	A1	20040219	WO 2003-US25341	20030812

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004110755 A1 20040610 US 2003-638702 20030811
PRIORITY APPLN. INFO.: US 2002-403115P P 20020813
GI



I

AB The invention relates to pharmaceutical combination therapies based on p38 kinase inhibitors and another active ingredients, pharmaceutical compns. comprising such combinations, processes for preparing them, and their use in the treatment of cytokine-mediated diseases. Preparation of I (BIRB 796 BS) is described.

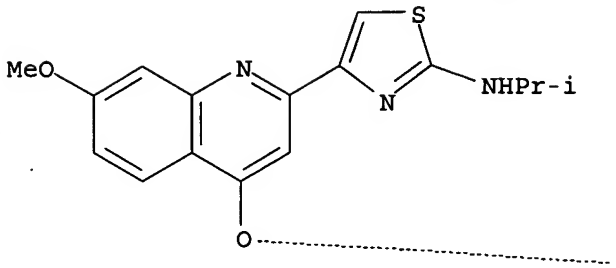
IT **300832-84-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

RN 300832-84-2 HCAPLUS

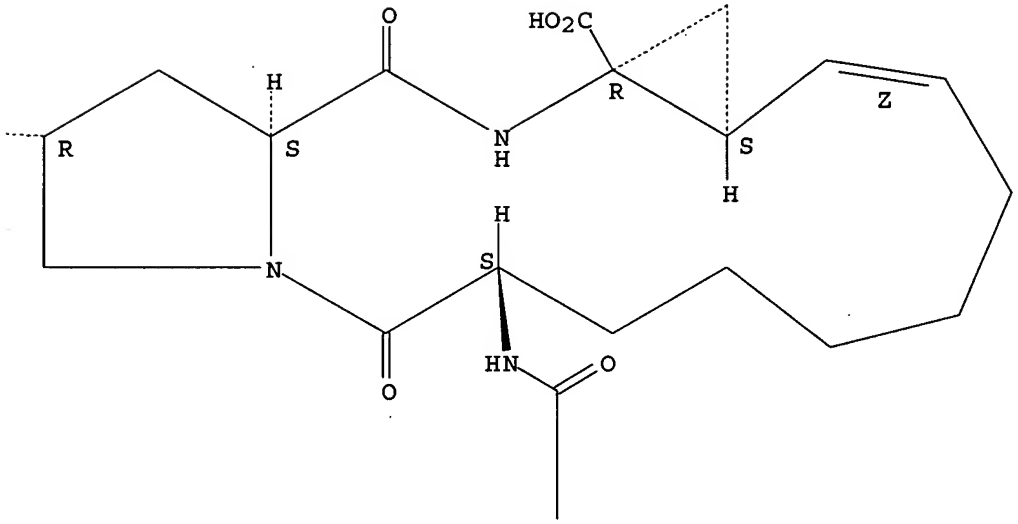
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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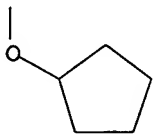


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:886572 HCAPLUS
DOCUMENT NUMBER: 140:122161
TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
AUTHOR(S): Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray;

Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre; Boes, Michael; Cameron, Dale R.; Cartier, Mireille; Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau, Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace, Lisette; LaPlante, Steven R.; Narjes, Hans; Poupart, Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St. George, Roger; Simoneau, Bruno; Steinmann, Gerhard; Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven M.; Yong, Chan-Loi; Llinas-Brunet, Montse

CORPORATE SOURCE: Departments of Biological Sciences, Boehringer Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.

SOURCE: Nature (London, United Kingdom) (2003), 426(6963), 186-189
CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of BILN 2061, a small mol. inhibitor biol. available through oral ingestion and the first of its class in human trials. Administration of BILN 2061 to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

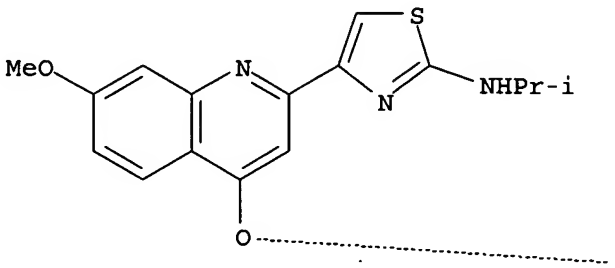
IT **300832-84-2**, BILN 2061
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)

RN 300832-84-2 HCAPLUS

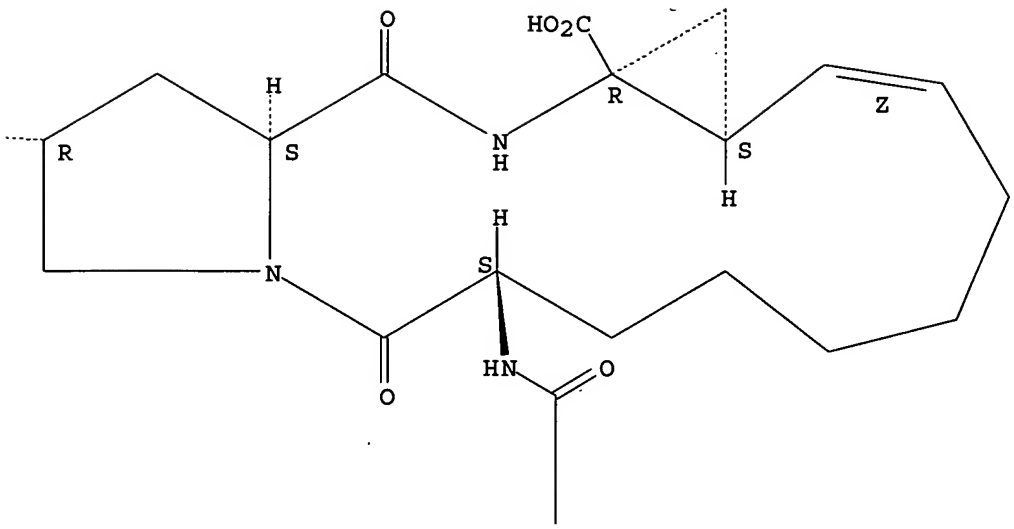
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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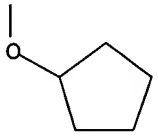


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:648255 HCAPLUS
DOCUMENT NUMBER: 139:197768
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-Marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-Brunet, Montse
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: U.S., 90 pp., Cont.-in-part of U.S. Ser. No. 542,675, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

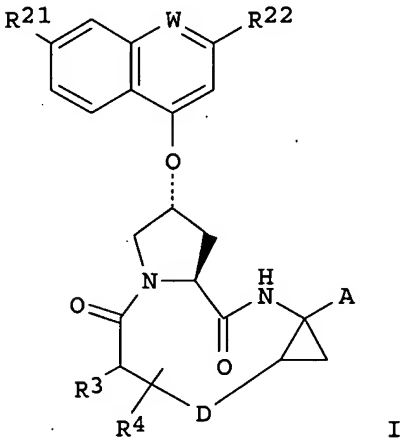
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6608027	B1	20030819	US 2001-760946	20010116
EP 1437362	A1	20040714	EP 2004-9264	20000403

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY

US 2004002448	A1	20040101	US 2003-358726	20030205
PRIORITY APPLN. INFO.:			US 1999-128011P	P 19990406
			US 2000-542675	B2 20000403
			EP 2000-913999	A3 20000403
			US 2001-760946	A1 20010116

OTHER SOURCE(S): MARPAT 139:197768

GI



I

AB Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

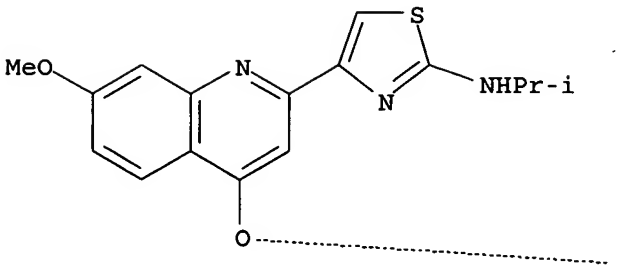
IT **300832-84-2P 300832-97-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCAPLUS

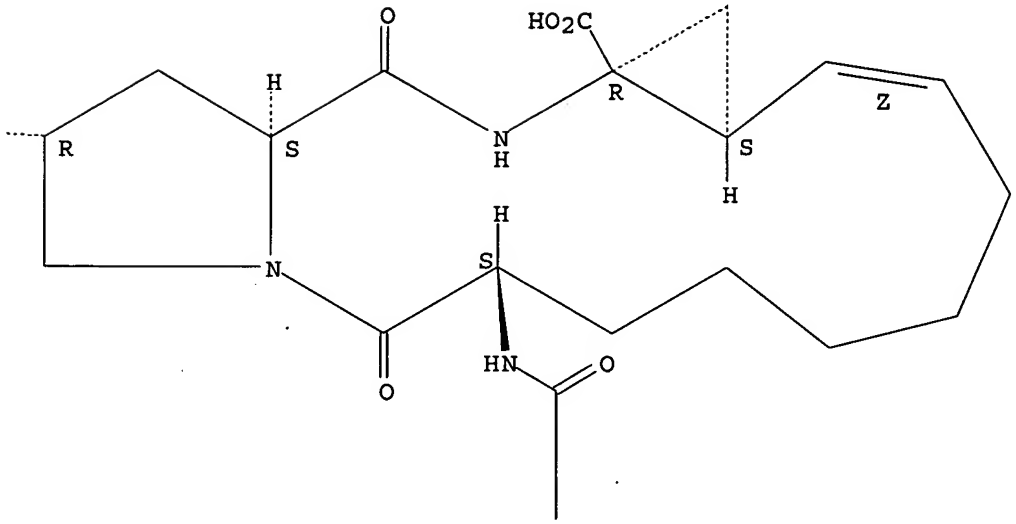
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

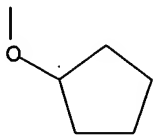
PAGE 1-A



PAGE 1-B



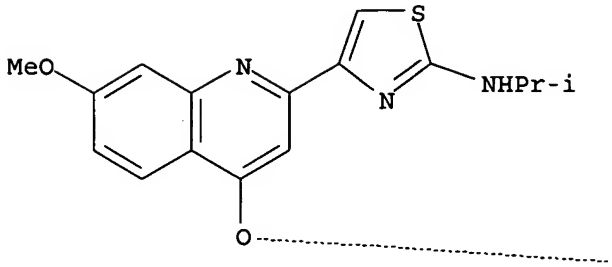
PAGE 2-B



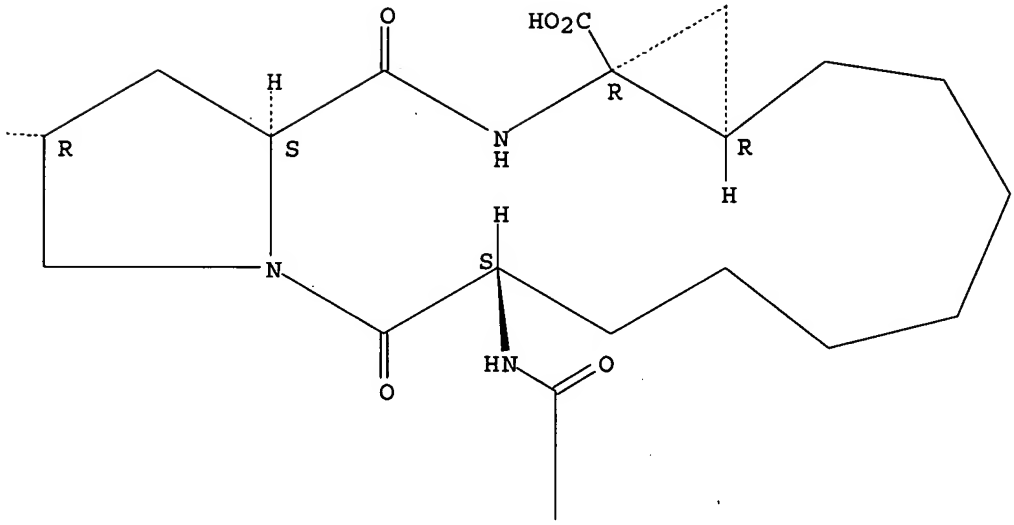
RN 300832-97-7 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,13aR,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

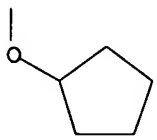
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633516 HCAPLUS
DOCUMENT NUMBER: 139:185670
TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors
INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066103	A1	20030814	WO 2003-US3380	20030205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003195228	A1	20031016	US 2003-357919	20030204
EP 1474172	A1	20041110	EP 2003-707713	20030205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-355694P	P 20020207
			WO 2003-US3380	W 20030205

OTHER SOURCE(S): MARPAT 139:185670
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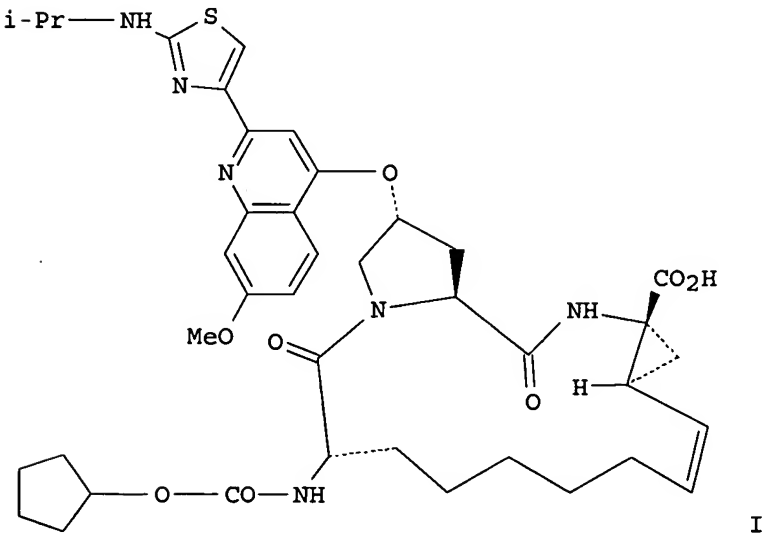


I

AB Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors having improved bioavailability, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. include co-solvent systems, lipid based systems, solid dispersions and granulations, and all comprise the hepatitis C viral protease inhibitor, at least one pharmaceutically acceptable amine and optionally one or more addnl.

ingredients. A composition contained I 4, tromethamine 3.2, water 44.8, ethanol 21.3, and propylene glycol 26.7 weight/weight%.

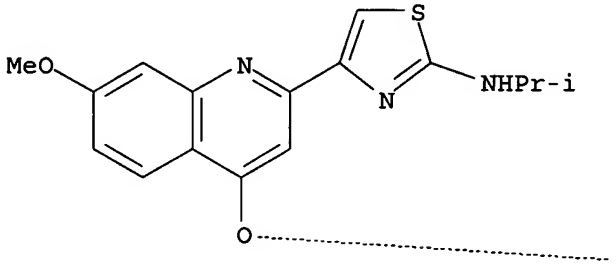
IT **300832-84-2**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease inhibitors)

RN 300832-84-2 HCAPLUS

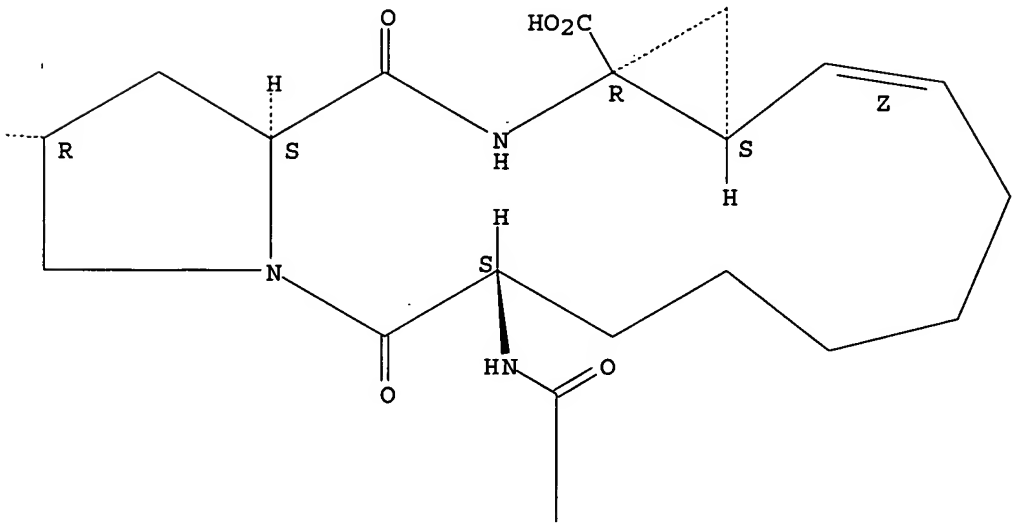
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

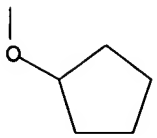
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511084 HCAPLUS
DOCUMENT NUMBER: 139:69527
TITLE: Preparation of macrocyclic compounds as inhibitors of hepatitis C virus
INVENTOR(S): Campbell, Jeffrey Allen; Good, Andrew Charles
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053349	A2	20030703	WO 2002-US39926	20021213
WO 2003053349	A3	20040115		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004038872	A1	20040226	US 2002-317451	20021212
EP 1455809	A2	20040915	EP 2002-795860	20021213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:
US 2001-344080P P 20011220
US 2002-382103P P 20020520
WO 2002-US39926 W 20021213

OTHER SOURCE(S): MARPAT 139:69527
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to macrocyclic compds. I [R1 = (cyclo)alkyl; R2 = H, halo, alkyl, alkoxy, cycloalkoxy, (un)substituted aryl or heterocyclyl; R3 = H, halo, CF3, alkoxy, cycloalkoxy; R4 = NH2 or NHR6, where R6 is alkanoyl, alkylaminocarbonyl, or carbalkoxy; Q is a 3-9 atom (un)saturated alkylene chain optionally containing 1-3 heteroatoms O, S, SO, or SO2], including methods for their synthesis and use in pharmaceutical compns. for therapeutic or prophylactic prevention or treatment of hepatitis C

virus (HCV) infection. Thus, 3,13-diazatricyclo[11.3.0.04,6]hexadec-7-ene derivative II was prepared by a multistep procedure and assayed for inhibition of HCV NS3/4A protease (IC50 < 5 μM).

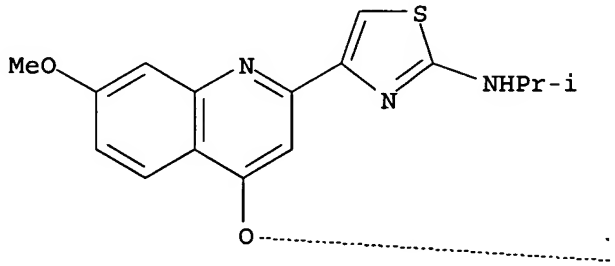
IT **300832-84-2P 552335-68-9P 552335-69-0P 552335-70-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

RN 300832-84-2 HCAPLUS

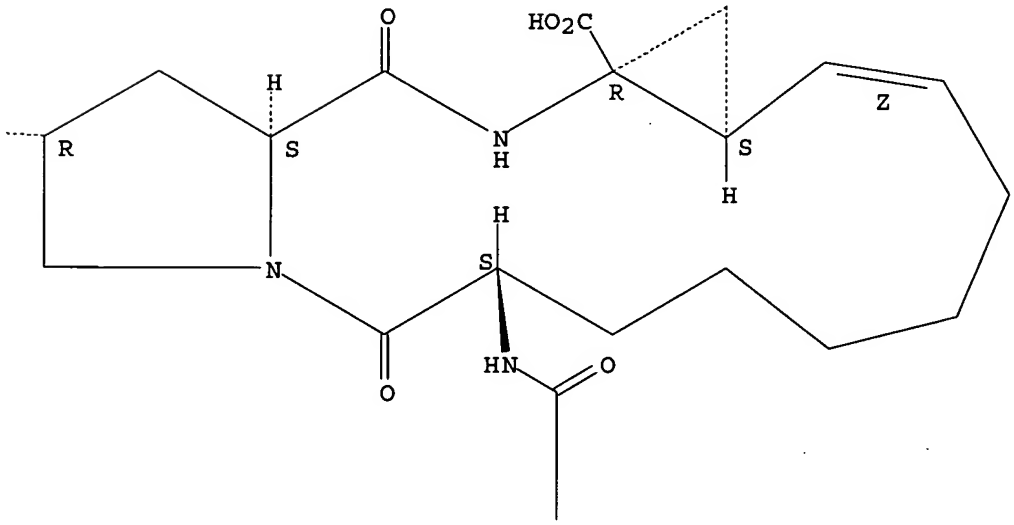
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R;6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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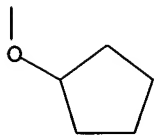
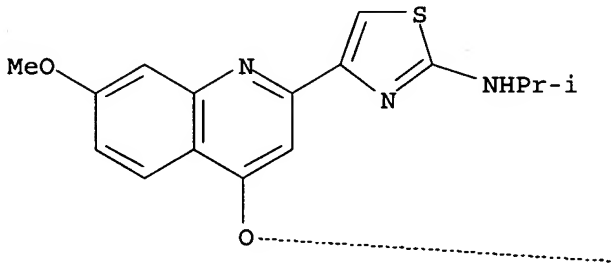


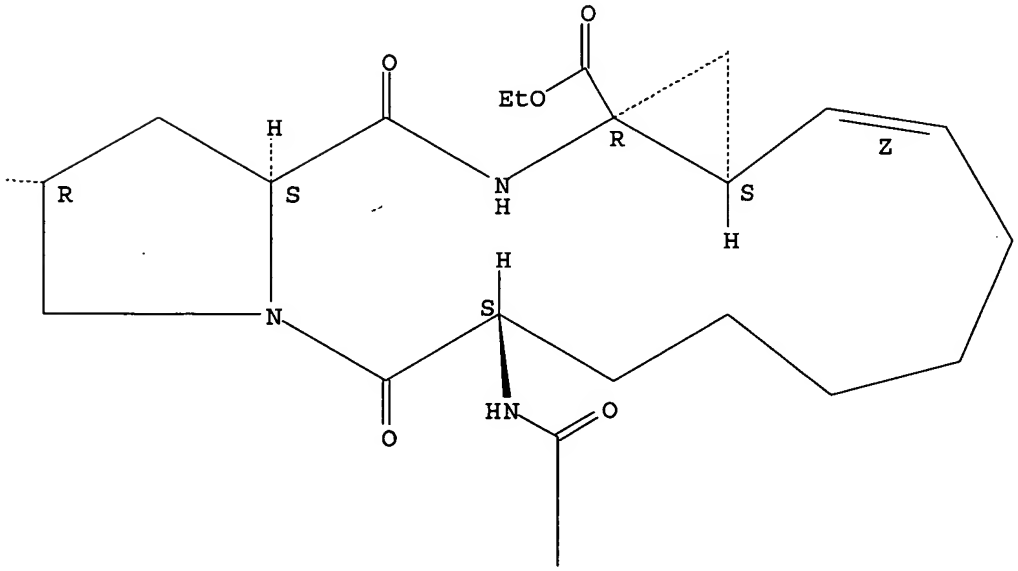
RN 552335-68-9 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, ethyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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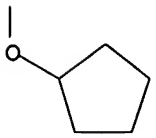
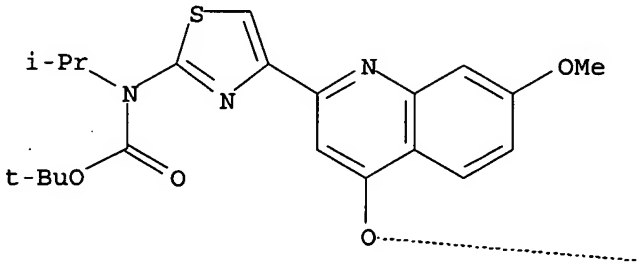


RN 552335-69-0 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-2-[[2-[2-[[(1,1-dimethylethoxy)carbonyl](1-methylethyl)amino]-4-thiazolyl]-7-methoxy-4-quinolinyl]oxy]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-5,16-dioxo-, ethyl ester, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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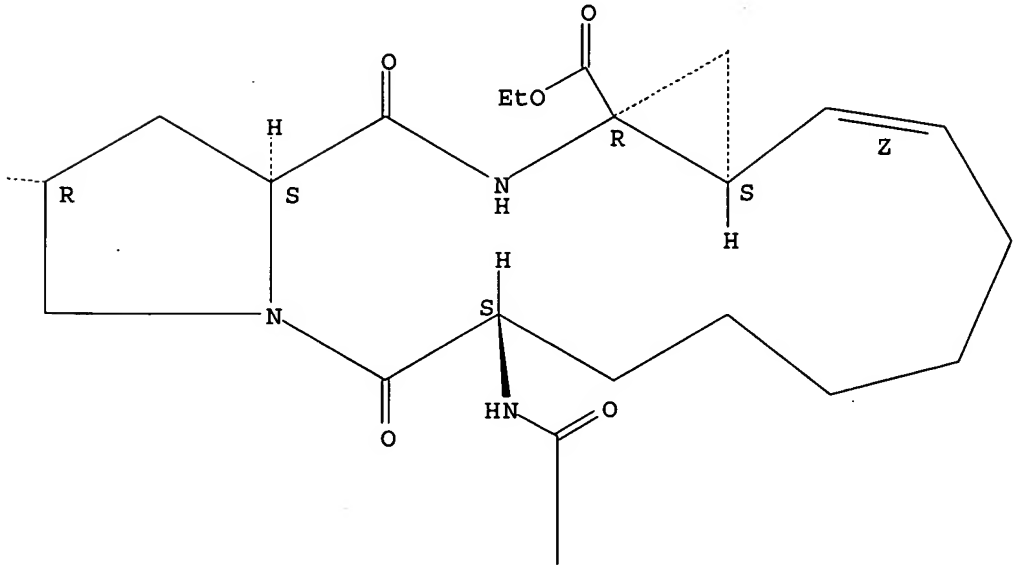
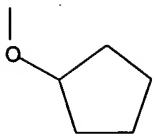


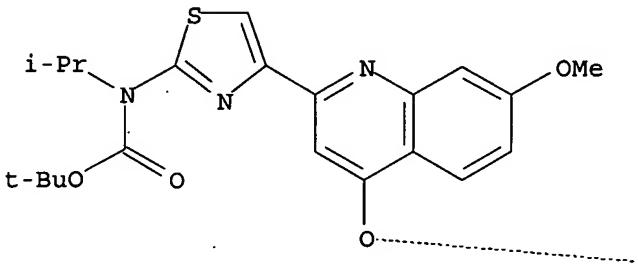
PAGE 2-B



RN 552335-70-3 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-2-[[2-[2-[[(1,1-dimethylethoxy)carbonyl](1-methylethyl)amino]-4-thiazolyl]-7-methoxy-4-quinolinyl]oxy]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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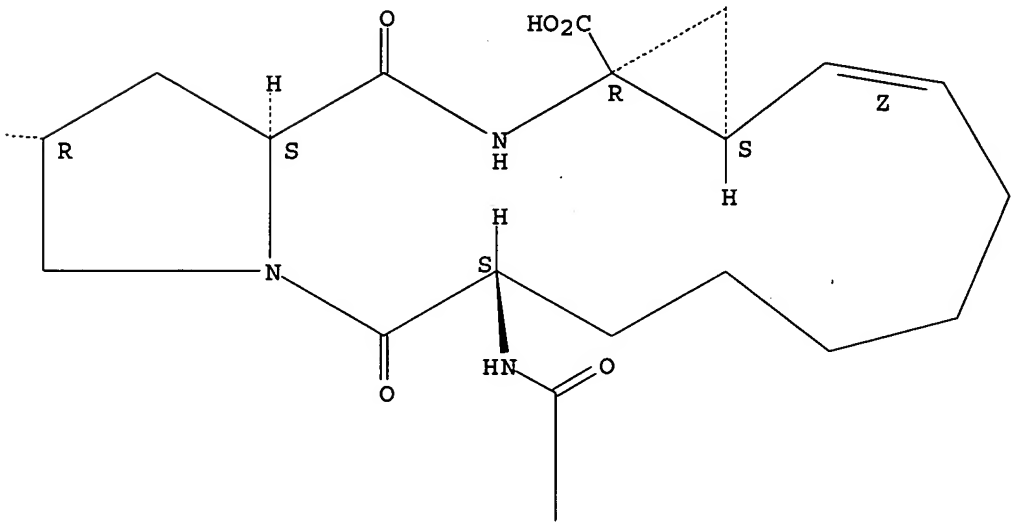

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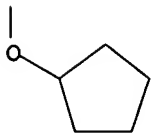
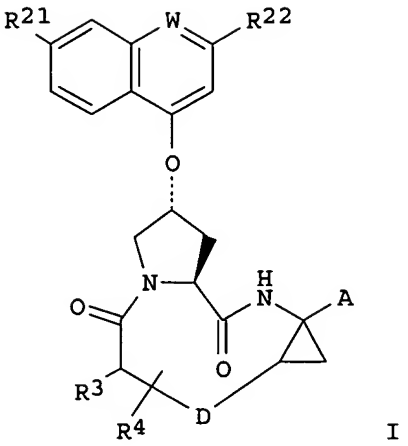


L8 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:725652 HCAPLUS
DOCUMENT NUMBER: 133:296659
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-brunet, Montse
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000059929	A1	20001012	WO 2000-CA353		20000403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2367127	AA	20001012	CA 2000-2367127		20000403
EP 1169339	A1	20020109	EP 2000-913999		20000403
EP 1169339	B1	20040929			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 2000009599	A	20020115	BR 2000-9599		20000403
TR 200102878	T2	20020121	TR 2001-200102878		20000403
EE 200100516	A	20021216	EE 2001-516		20000403
NZ 515286	A	20040227	NZ 2000-515286		20000403
EP 1437362	A1	20040714	EP 2004-9264		20000403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY					
AT 277945	E	20041015	AT 2000-913999		20000403
BG 105970	A	20020531	BG 2001-105970		20011002
HR 2001000720	A1	20021231	HR 2001-720		20011004
NO 2001004857	A	20011031	NO 2001-4857		20011005
PRIORITY APPLN. INFO.:			US 1999-128011P	P	19990406
			EP 2000-913999	A3	20000403
			WO 2000-CA353	W	20000403

OTHER SOURCE(S): MARPAT 133:296659
GI



I

AB Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus . Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

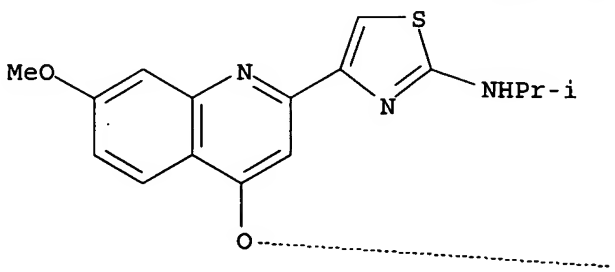
IT **300832-84-2P 300832-97-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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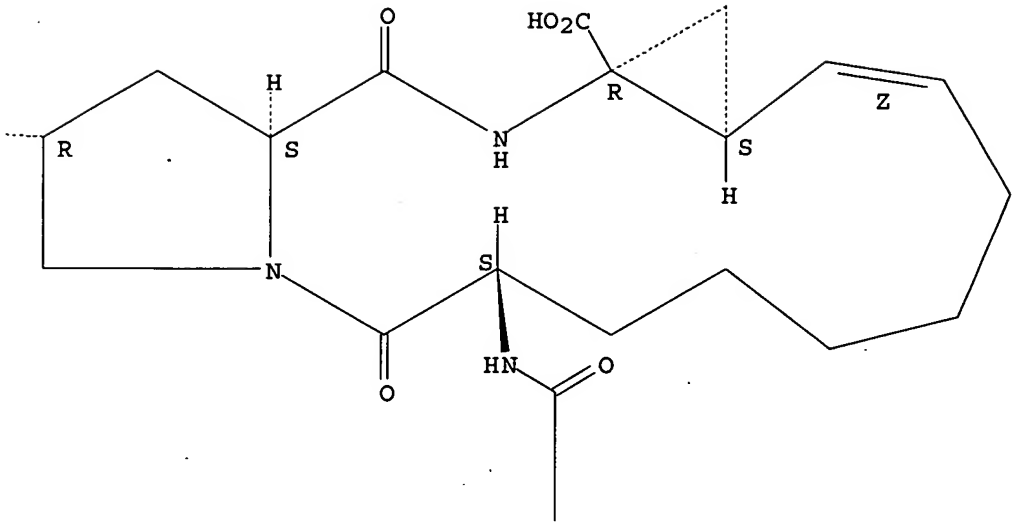

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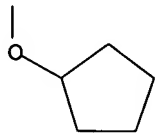
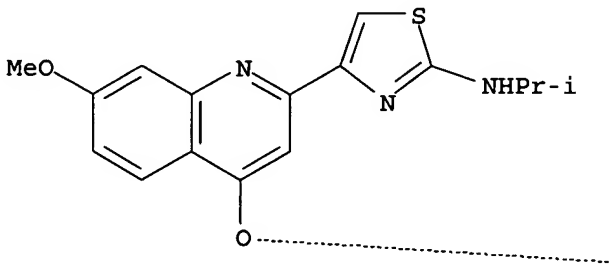


RN 300832-97-7 HCAPLUS
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]amino]hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,13aR,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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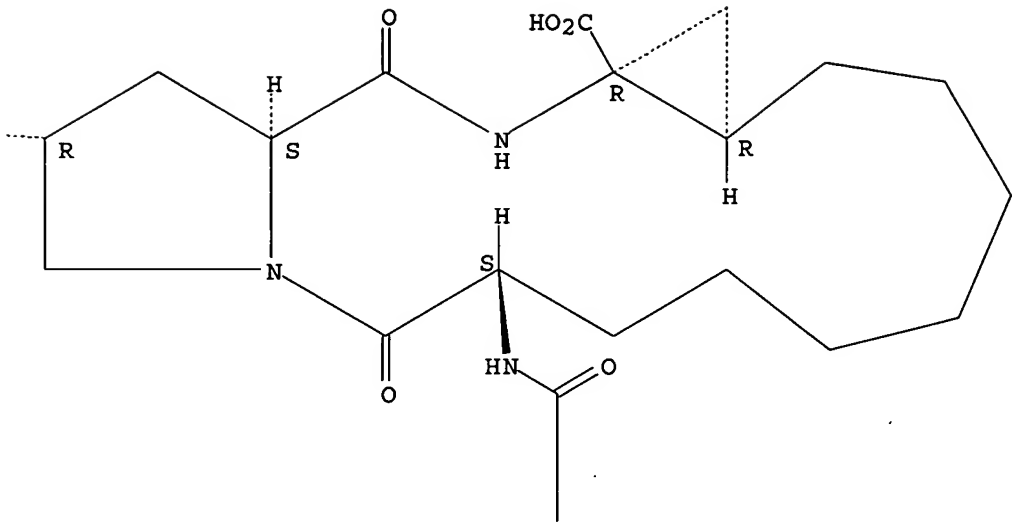

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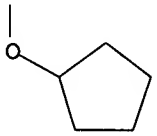

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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